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Review

Endoplasmic reticulum stress and protein quality control in diabetic cardiomyopathy☆

Lifang Yang [a,c,1], Dajun Zhao [b,1], Jun Ren [c,*], Jian Yang [b,**]

[a] Department of Anesthesiology, Xijing Hospital, The Fourth Military Medical University, Xi'an 710032, China
[b] Department of Cardiac Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an 710032, China
[c] Center for Cardiovascular Research and Alternative Medicine, University of Wyoming, Laramie, WY 82071, USA

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ABSTRACT

Endoplasmic reticulum (ER) stress, together with the unfolded protein response (UPR), is initially considered an adaptive response aiming at maintenance of ER homeostasis. Nonetheless, ER stress, when in excess, can eventually trigger cell apoptosis and loss of function. UPR is mediated by three major transmembrane proteins, including inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor (ATF) 6. A unique role has been speculated for ER stress in the pathogenesis of diabetes mellitus (DM) and its complications. Recent studies have shown that ER stress is an early event associated with diabetic cardiomyopathy, and may be triggered by hyperglycemia, free fatty acids (FFAs) and inflammation. In this mini-review, we attempted to discuss the activation machinery for ER stress in response to these triggers en route to disrupted ER function and cellular autophagy or apoptosis, ultimately insulin resistance and development of diabetic cardiomyopathy. This article is part of a Special Issue entitled: Autophagy and protein quality control in cardiometabolic diseases.

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1. Introduction

Diabetes mellitus (DM) is a chronic, progressive metabolic disorder characterized by deficiency of insulin secretion, loss of insulin sensitivity or both, resulting in elevated plasma glucose levels. Individuals with DM display an increased risk for macro- and micro-vascular complications [1,2]. These vascular injuries often coexist and contribute to the onset and progression of hypertension, ischemia as well as diastolic/systolic dysfunction [3]. Moreover, cardiovascular complications account for the high morbidity and mortality in diabetic populations. When compared to the age-matched controls, the relative risk of heart failure is 2-fold greater in diabetic males, and 5-fold greater in diabetic females, independent of age, ethnicity, body mass, dyslipidemia and coronary artery disease according to the Framingham Heart Study [4]. Diabetic cardiomyopathy is a distinct myocardial disease in patients with DM, leading to the structural and functional changes in the heart independently of hypertension, coronary artery and valvular heart disease [5]. These changes can eventually result in left ventricular hypertrophy (LVH) and diastolic/systolic dysfunctions [6]. An array of chronic and complex changes have been identified at the molecular level, contributing to the etiology of diabetic cardiomyopathy such as perturbations of intracellular energy metabolism, alterations in intracellular ion homeostasis and oxidative stress [7–9]. More recently, ER stress was suggested to contribute to the onset and progression of diabetic cardiomyopathy [10,11]. Nevertheless, the precise interplay among ER stress, development of cardiac hypertrophy and progression to heart failure still remains elusive.

ER is an organelle with rough and smooth regions. The rough region of membrane forms stacks of flattened cisternae and is composed of a membrane-enclosed lumen. The smooth region of membrane is connected to these membranous cisternae to form a fine network of tubules. Polypeptide chains of secreted, transmembrane and luminal proteins synthesize, fold and mature in the ER lumen [12]. It also serves as a site for lipid biosynthesis and Ca^{2+} storage [13]. Nascent polypeptides are transferred into the ER lumen, undergoing posttranslational modifications and rounds of folding interactions in order to optimize their functions. Correctly folded proteins then move away from the ER to remote intracellular organelles and the extracellular surface, while misfolded proteins are either retained within the ER or subject to degradation by cytoplasmic proteasomes [14].

Efficient ER function relies heavily on numerous quality control factors, such as molecular chaperones, folding enzymes and a Ca^{2+}-rich environment [15]. When ER homeostasis is aberrant under the conditions of radiation, hypoxia, ischemia, oxidation or dysregulation of Ca^{2+}, ER stress response will be triggered to cope with this imbalance,

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* Correspondence to: J. Ren, University of Wyoming College of Health Sciences, Laramie, WY 82071, USA. Tel.: +1 307 766 6131; fax: +1 307 766 2953.
** Corresponding author. Tel.: +86 13892828016; fax: +86 29 83210092.
E-mail addresses: jren@uwyo.edu (J. Ren), yangjian1212@hotmail.com (J. Yang).

[1] The first 2 authors contributed equally to this paper.

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which is also termed as the UPR [12]. It was first described by Kozutsumi in 1988 as an adaptive mechanism to increase the protein folding capacity as well as to decrease the unfolded protein load [16]. The UPR aims to restore the ER homeostasis by (1) decreasing the load of proteins in the ER via translational attenuation, (2) increasing the transcription of chaperones and other proteins involved in the folding and maturation of proteins, and (3) inducing the degradation of misfolded proteins via the ER-associated degradation (ERAD) complex [17]. If it fails, ER initiates the death signaling pathways [18].

In this mini-review, we will attempt to discuss the possible mechanisms behind the potential contribution of ER stress and UPR in the pathogenesis of diabetic cardiomyopathy, in an effort to provide some evidence for the potential UPR-targeted therapies for this disease.

2. Protein quality control and signaling pathways of the UPR

Quality control is a complicated mechanism that maintains the protein biosynthesis with properly folded and assembled structures in the ER [19]. It relies on molecular chaperones and folding enzymes to monitor and assist the folding process. These chaperones and enzymes can be classified into three major groups: (1) binding protein/glucose regulated protein (BiP/GRP) 78, GRP94, (2) calnexin (CNX) and calreticulin (CRT), (3) protein disulfide isomerase, such as ER protein (ERp) 57 and ERp72 [15]. GRP78 and GRP94 have the ability to recognize exposed hydrophobic regions, a common feature of nascent misfolded proteins, thus assisting protein folding and assembling [20]. CNX and CRT interact with glycoproteins via their lectin binding ability, allowing folding and interacting with enzymes [21,22]. ERp57 uses the oxidative environment of the ER to generate disulfide linkages, which are directly affected by the primary donor of the energy [23]. If quality control is unable to fold the protein, the UPR will be triggered by the continuous accumulated unfolded/misfolded proteins in three transmembrane protein-mediated signaling pathways, namely inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase(PERK) and activating transcription factor (ATF) 6 pathways (Fig. 1) [24]. Under physiological conditions, these sensors are maintained in an inactive state by binding to GRP78, while ER stress increases the binding of BiP to the luminal misfolded proteins, and the resultant sequestration away from IRE1, PERK and ATF6 usually leads to the activation of these ER stress signaling molecules [25].

2.1. IRE1 signaling pathway

IRE1 is consist of an N-terminal luminal sensor domain, a single transmembrane domain and a C-terminal cytosolic effect or region which manifests both kinase and endoribonuclease activity [26]. There are two isoforms of IRE1 namely IRE1α and -1β. The UPR is mainly governed by IRE1α. Upon activation, IRE1α mediates an unconventional cytoplasmic splicing, to remove a 26-nucleotide intron from X-box-binding protein 1 (XBP1) mRNA, yielding a fusion protein XBP1s [27]. XBP1s act as a potent transcription factor for the expression of potential UPR target genes, to upregulate the ER chaperones, components of the ERAD complex and the biosynthesis of phospholipid, and to export and degrade misfolded proteins in an effort to resolve ER stress [28]. IRE1 activates Jun N terminal kinase (JNK) by recruiting the apoptosis signal-regulating kinase 1 (ASK1), caspase-12 and tumor necrosis factor receptor-associated factor 2 (TRAF2), which are pro-apoptotic [29].

Many cell metabolism modulators regulate the IRE1 pathway. IRE1α is phosphorylated by PKA, to control the glucagon-mediated expression of gluconeogenic genes [30]. Both XBP1 splicing and JNK activation are controlled by the mammalian target of rapamycin complex 1 (mTORC1), the major sensor of nutrient and energy in cells [31,32]. P85, a repressive regulatory subunit of PI3K, also interacts with XBP1, increasing its nuclear translocation and transcriptional activity [33].

2.2. PERK signaling pathway

PERK is a type 1 transmembrane protein that possesses a luminal domain similar to that of IRE1, and a cytoplasmic portion that possesses protein serine/threonine kinase activity. It has a PEK-like catalytic

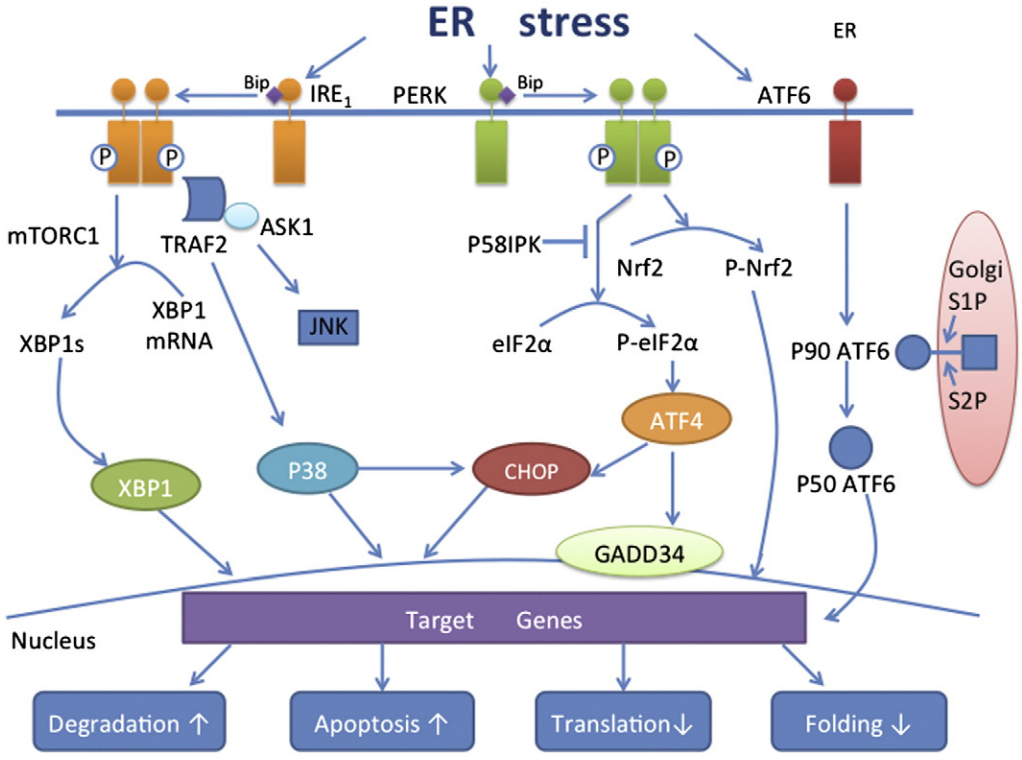

Fig. 1. When ER is unable to fold secretory and membrane proteins, the accumulated unfolded/misfolded proteins trigger the UPR in three transmembrane protein-mediated signaling pathways, as IRE1, PERK and ATF6 pathways.

domain, which phosphorylates the eukaryotic translation initiation factor 2α (eIF2α) [34]. P58^{IPK}, one of the heat shock protein 40 (HSP40) family members, regulates PERK by binding to the kinase domain of the sensor and decreasing eIF2α phosphorylation [35]. This regulation affects the expression of its downstream targets, reducing the translation of the UPR target proteins BiP and C/EBP homologous protein (CHOP) [36].

When activated, PERK phosphorylates α-subunit of eIF2α on serine-51, down regulating cap- or eIF2α-dependent translation, thus shutting off global mRNA translation [37]. The inhibition of global translation reduces the protein-folding load on the ER and allows the cell to focus resources on resolving the ER stress, thus facilitating survival. In contrast to inhibition of general mRNA translation, the PERK/eIF2α pathway stimulates the translation of several specific mRNAs containing multiple 53-upstream open reading frames, such as ATF4, CHOP and growth arrest and DNA damage (GADD) 34 [38]. PERK also phosphorylates nuclear factor (erythroid-derived 2)-related factor2 (Nrf2), resulting in its translocation to the nucleus where it turns on expression of oxidative genes in response to oxidative stress [39]. Therefore, this signaling pathway of the UPR acts to preserve redox balance during ER stress through activation of ATF4 and Nrf2. In addition to its role in ER stress, PERK also takes part in the activation of autophagy as a survival mechanism during episodes of nutrient deprivation, hypoxia and radiation [40,41].

2.3. ATF6 signaling pathway

ATF6, also known as basic leucine zipper protein (bZIP), is an ER-associated type 2 transmembrane protein with three structural domains: a luminal C-terminal, a transmembrane and a cytoplasmic N-terminal domain. Two isoforms have been described: ATF6α and ATF6β. In the luminal domain, ATF6 has Golgi localization sequences (GLS), two in the ATF6α isoform (GLS1 and GLS2) and one (GLS2) in the ATF6β isoform [42]. Under basal conditions, ATF6 is retained in the ER via interaction with the chaperone BiP/GRP78 and CRT [43]. During the ER stress, ATF6α and ATF6β are released from BiP prior to translocation to the Golgi complex [44], where they are cleaved by Golgi-resident proteases, first by site 1 protease (S1P) and then in the intramembrane region by S2P [45]. These intra-membrane proteases were initially implicated in the cleavage of the transcription factor steroid regulatory element-binding protein (SREBP), involved in lipid metabolism. The cleaved-off cytoplasmic domain is a transcriptional activator of genes involved in ERAD, lipid biosynthesis, protein folding and ER expansion [46].

A series of ATF6 homologues have been identified that undergo similar processing at the Golgi and possess tissue-specific roles, including cAMP responsive element-binding protein (CREB) H, CREB3 (Luman), CREB3L1 (Oasis), CREB3L2 (BBF2H7) and CREB4 (Tisp40) [12]. CREB3 is expressed in monocytes and dendritic cells and CREB3L1 is highly expressed in astrocytes and osteoblasts. Although it is reported to participate in the expression of numerous genes involved in the ERAD, the pathophysiological triggers and mechanisms behind activation of such sensor remain somewhat elusive [47].

3. ER stress in the complications of DM

3.1. ER stress in metabolic disorder

ER stress can be activated in response to metabolic syndrome in multiple organs, including the hypothalamus, liver, adipose tissue, muscle and pancreatic β cells (Fig. 2) [48]. The hypothalamus regulates caloric intake and energy expenditure in response to signals delivered by leptin, insulin, nutrients and gut hormones [49], whereas hypothalamic ER stress leads to inflammation and leptin/insulin resistance. M. Milanski and colleagues demonstrated that hypothalamic ER stress occurred upon the activation of toll-like receptor (TLR) 4 signaling, the effect of which could be reversed by genetic or pharmacological disruption of TLR4 by both in vivo (rats) and in vitro (isolated hypothalamic tissues) studies [50]. This finding received convincing support from other studies as well [51,52]. Chronic hepatic ER stress is wildly conceived to promote the onset and development of insulin resistance in obese animals and humans [53–55]. ER stress in adipose tissues inhibits insulin signaling, represses lipolysis, and alters secretion of adipokines, such as insulin receptor substrate (IRS) 1 and IRS2 [56]. In a recent clinical study comparing various fat depots, BiP and XBP1 were highly expressed in visceral compared with subcutaneous fat, and more pronounced in severe obesity [57]. Liu and coworkers showed that decreased ER disulfide-bond A oxidoreductase-like (DsbA-L) protein expression compromised adiponectin folding and multimerization, leading to ER stress in obesity [58,59]. ER stress also inhibits resistin transcription in murine adipocytes through upregulation of CHOP [60]. Saturated fats cause ER stress in muscles while prolonged ER stress impairs insulin synthesis and triggers apoptosis in pancreatic β cells [61–64].

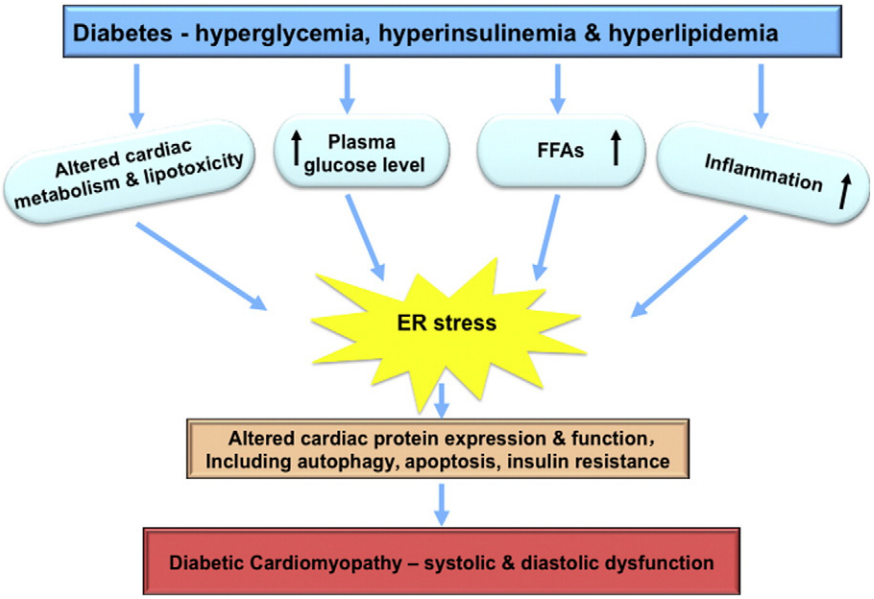

Fig. 2. ER stress gets activated in numerous organs of metabolic syndrome, including the hypothalamus, liver, adipose tissue, muscle and pancreatic β cells as well as the heart.

3.2. ER stress in the diabetic heart

Diabetes mellitus is usually accompanied with cardiac hypertrophy, inflammation, interstitial fibrosis, aberrant intracellular Ca^{2+} handling, endothelial dysfunction and defective substrate metabolism. Disturbed cardiomyocyte hemostasis may facilitate ER stress and the UPR to participate in the onset and progression of cardiomyocyte hypertrophy and heart failure by modulating ATP, ER Ca^{2+}, and UDP-glucose. Quality control changes its molecular chaperones in order to reverse the onset and progression of diabetic cardiomyopathy. First of all, in vivo evidence depicted an increase in the synthesis of BiP/GRP78, accompanied with the activation of the XBP1, IRE1α/TRAF2 signal cascades in pressure overload elicited hypertrophy [65,66]. Mao and coworkers demonstrated that autoimmune cardiomyopathy induced by β_1-adrenergic receptor peptide was associated with an increase of ATF6 cleavage as well as nuclear translocation, which might then lead to ER stress [67]. CHOP knockout mice displayed a less pronounced hypertrophy and cardiac dysfunction in comparison with wild type animals [68]. Transgenic mice expressing a mutant of KDEL receptor or expressing a dominant negative mutant of ATF6 showed dilated cardiomyopathy, enhanced expression of CHOP and compromised cardiac function [69,70]. Furthermore, clinical trial observed that human sarco/ER Ca^{2+}ATPase (SERCA) 3f up-regulated in failing hearts from patients with diverse cardiomyopathies and the overexpression of SERCA3f paralleled an increase in ER stress markers, such as processing of XBP1 and GRP78 [71]. All these studies suggest that ER stress is induced in the diabetic heart and the UPR-associated metabolic disturbances altered Ca^{2+} handling, oxidative stress and apoptosis participate in the pathogenesis of diabetic cardiomyopathy [72].

4. Triggers of ER stress in the diabetic cardiomyopathy

Pathological cardiac hypertrophy in diabetic cardiomyopathy is accompanied with alterations in both intracellular Ca^{2+} homeostasis and metabolism, which, together with increased protein synthesis, can induce ER stress and consequently trigger the UPR. Three likely major triggers have been postulated to induce ER stress including hyperglycemia, FFAs and inflammation (Fig. 3).

4.1. Hyperglycemia

Hyperglycemia represents one of the principal drivers for metabolic, functional and structural alterations present in diabetic hearts. Aberrations in glucose control cause a series of changes in the microenvironment of cardiomyocyte, including deletion of glucose transporter 4 (GLUT4), generation of reactive oxygen species (ROS), alteration of Ca^{2+} level and hyperinsulinemia and insulin resistance. All these changes alter the homeostasis of ER, which finally trigger UPR. As hyperglycemia becomes chronic in diabetes, glucose that normally serves as fuel or substrate is used to generate detrimental metabolites for cardiomyocyte. Lakshmanan and colleagues proved that hyperglycemia-stimulated myocardial ER stress contributes to diabetic cardiomyopathy. After further study, they showed that PERK and ATF6 pathways were activated, whereas IRE1α-XBP1 pathway was not activated in

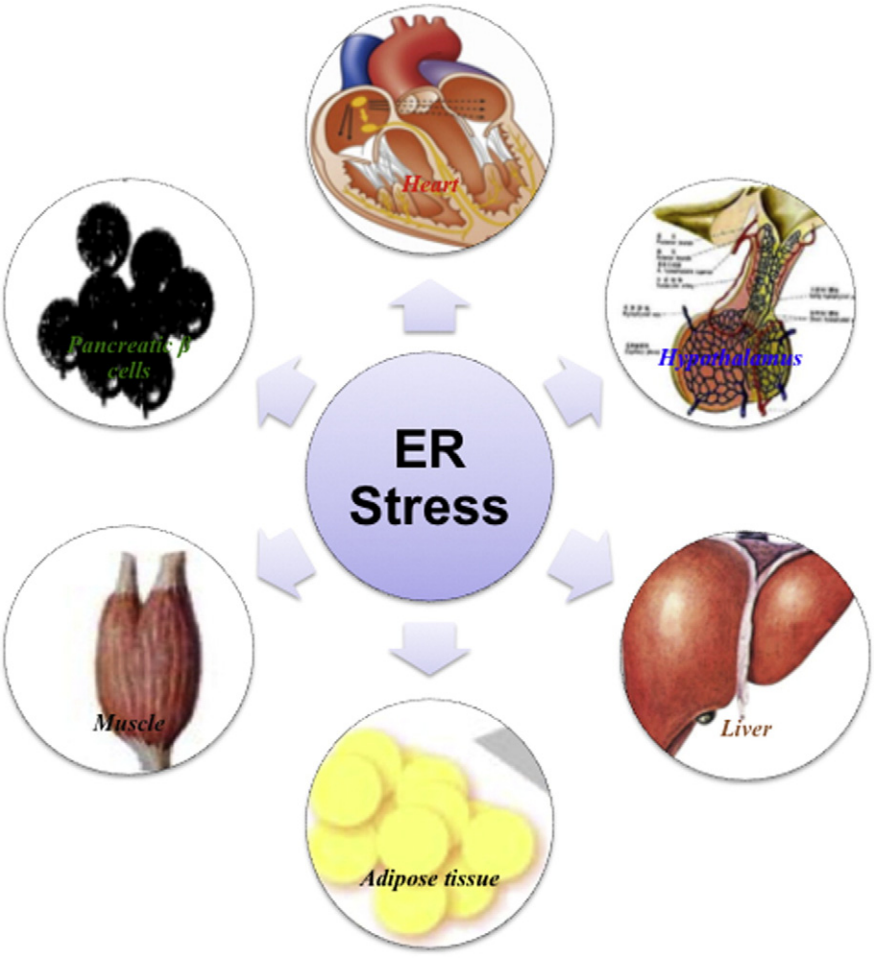

Fig. 3. Diabetes causes high plasma glucose level, elevating the amount of FFAs, activating the inflammation and altering cardiac metabolism and lipotoxicity as well, which trigger ER stress, disrupt ER function and cause cell autophagy or apoptosis as well as insulin resistance, thus finally leading to diabetic cardiomyopathy.

the transgenic non-obese type 2 diabetic rats. It was evidenced by the significantly up-regulated expression of the sub-arm of UPR signaling proteins, such as p-PERK, p-eIF2α, ATF6, CHOP/GADD153, TRAF2 [73]. UPR was found to be intact in high fat diet (HFD) fed rats as evidenced by increased PERK phosphorylation and GRP78 levels in relation to the primary ER client proteins insulin and islet amyloid polypeptide (IAPP) [74]. Moreover, alleviated ER stress is noted when hyperglycemia and glucose intolerance are improved [75].

4.2. FFAs

FFAs are the primary energy substrate used by the heart and are supplied to cardiac cells via serum, lipoproteins or lipolysis of triglycerides in the heart. The abnormal state of energy metabolism in the diabetic heart leads to an increased amount of fatty acid extraction and storage. Indeed, hearts from diabetic and/or obese animals show an over reliance on FFAs for energy production and have accelerated rates of fatty acid oxidation [76].

High level of FFAs in the circulation and cells may trigger a series of unfavorable stress responses in cardiomyocyte including ER stress. Li and colleagues reported that accumulation of saturated FFA-containing phospholipids inhibits SERCA2b activity because of a loss in membrane fluidity caused by increased ordering of the ER membrane [77], thereby causing Ca^{2+} depletion and protein misfolding. Boslem also showed that FFAs induced the depletion of ER Ca^{2+} and impeded protein trafficking by ceramide synthesis [78]. Pulinilkunnil and colleagues demonstrated that FFAs induced cardiomyocyte apoptosis in type 1 diabetic Akita mice through upregulation of CHOP and activation of JNK. With cardiac-specific overexpression of the adipose triglyceride lipase in mice, expression of cardiac ER stress biomarkers of GRP94, CHOP, CRT, CNX, phosphorylated PERK Thr^{980}, p38 mitogen activated protein kinases (MAPK) phosphorylation, and p38MAPK was reduced [79]. Prolonged type 2 DM can activate UPR in response to hyperglycemia although FFAs may trigger cardiac ER stress early on lipotoxic cardiomyopathy.

4.3. Inflammation

In the progress of diabetic cardiomyopathy, macrophages, neutrophils, mast cells, blood platelets and T cells are quickly activated in response to cardiovascular insults, a process commonly regarded as the inflammatory reaction [80]. For example, the presence of damaged cells and cell debris can induce activation of resident macrophages, leading to the release of pro-inflammatory cytokines and other molecules, like ROS and proteases, which cause damaging or protective effects on endothelial cells, smooth muscle cells and cardiomyocyte as well [81]. The inflammatory reaction is generally triggered by the activation of pattern recognition receptors, such as TLRs [50]. Fas ligands released by dying infiltrating inflammatory cells can initiate an intense inflammatory response, contributing to the onset and development of cardiomyopathy as well as heart failure [82,83].

Chronic infection and subsequent production of cytokines may lead to a several-fold amplification of inflammatory response in endothelial cells and cardiomyocyte, with increased ER stress and cell apoptosis [84,85]. It has been indicated that activation of TLR-signal can activate IRE1 with a permissive role for its downstream target XBP1 in the production of pro-inflammatory cytokines such as TNF-α, monocyte chemoattractant protein (MCP) 1 and interleukin (IL) -6, IL-8 in macrophages and endothelial cells, resulting in augmented TLR responses contributing to inflammation [86]. MCP-1 is an angiogenic factor associated with the recruitment of monocytic cells. Cardiac-specific expression of MCP-1 in mice causes inflammation and cell apoptosis [87]. Studies showed that ER stress response pathways, the UPR and ERAD, were highly activated in the hearts of MCP mice during the development of cardiovascular disease [88,89]. Different pro-inflammatory cytokines seem to preferentially affect different branches of the UPR, such as IL-1β induces Xbp1 splicing and PERK/eIF2α phosphorylation [90], while IFN-γ decreases expression of Xbp1s, Bip and several other ER chaperones downstream of ATF6/XBP1s, sensitizing cardiomyocyte to apoptosis induced by chemical ER stressors or IL-1 receptor [72].

Intra-myocardial contents of cytokines may disrupt the oxidative state of ER, resulting in the impairment of ER function and UPR. The oxidative state of the heart influences several proteins to disrupt energy utilization in the ER and activate the PERK/CHOP pathway, leading to the UPR [91]. These findings denote an important role for inflammation in the onset and progression of diabetic cardiomyopathy.

5. Role of ER stress in diabetic cardiomyopathy

ER stress responses, ER Ca^{2+} buffering, as well as protein and lipid turnover impact many cardiac functions, including energy metabolism, cardiogenesis, cardiac insulin resistance and heart failure.

5.1. Autophagy

Autophagy is a highly conserved cellular process for degradation and recycling of membranes, organelles, and cytoplasmic components in lysosomes. This process has been widely identified as an essential myocardial adaptive response to maintain energy homeostasis at both basal and stress conditions through a number of autophagy genes (Atgs) [92]. A plethora of stress conditions, including nutrient and energy starvation, oxidative stress, metabolic dysfunction and ER stress are observed to activate autophagy as a pro-survival pathway [93]. ER stress can induce autophagy in several canonical UPR pathways (Fig. 4). Ca^{2+} releases from the ER can stimulate different kinases that regulate autophagy. Ca^{2+}/calmodulin-dependent kinase kinase β (CaCMKKβ) phosphorylates and activates AMPK, leading to mTORC1 inhibition [94]. mTORC1 has been proposed to regulate autophagy by repressing the Atg1–Atg13–Atg101/FIP200 complex, thus inhibition of mTORC1 facilitates the initiation of autophagy [95–97]. The IRE1 arm of ER stress leads to JNK activation and increased phosphorylation of B cell lymphoma-2 (Bcl-2), which promotes its dissociation from Beclin-1 [98,99]. In addition, PERK-eIF2α-ATF4-dependent Atg12 upregulation is required for induction of autophagy in response to polyQ protein accumulation [100]. Recently, researchers suggest that ER stress may be both a trigger and consequence for autophagy. ER stress can induce autophagy in the UPR pathway mentioned above, while impaired autophagy may also contribute to ER stress. It has been suggested that restoration of autophagy alleviates obesity-induced ER stress [87,100].

In diabetic heart, ER stress may induce autophagy. Younce and colleagues demonstrated that hyperglycemia promoted MCP-1 production and MCP-1-induced protein (MCPIP) induction, leading to oxidative stress and activation of UPR. The MCPIP-induced UPR activation could upregulate IRE1, resulting in JNK activation and eventually autophagy. Prolonged autophagy finally led to cardiomyocyte apoptosis [87]. Our studies suggested that lessened phosphorylation of Akt-tuberous sclerosis complex (TSC), en route to dampened mTOR phosphorylation and then excess autophagy following thapsigargin challenge. These data indicate a role for Akt-mTOR-mediated autophagy in ER stress-induced cardiac anomalies [101]. The resultant cardiomyocyte contractile dysfunction can be reversed by heavy metal scavenger metallothionein. It significantly attenuated or ablated tunicamycin (TM)-induced elevation of autophagy markers or regulatory signals including phosphorylated serine/threonine-protein kinase (ULK1), Atg5, Atg7, light chain 3 (LC3) B-II, LC3B-II/LC3B-I ratio and p62 [102]. More recent findings have provided compelling evidence that mTOR kinase is an important regulator of myocardial autophagy and may serve as a converging point for the interplay between ER stress and autophagy [103]. mTORC1 may be operated both up- and down-stream of ER stress, to either enhance or suppress the anabolic output of mTORC1. However, in depth research is needed to clarify the precise interplay between ER stress and autophagy in the face of diabetic cardiomyopathy.

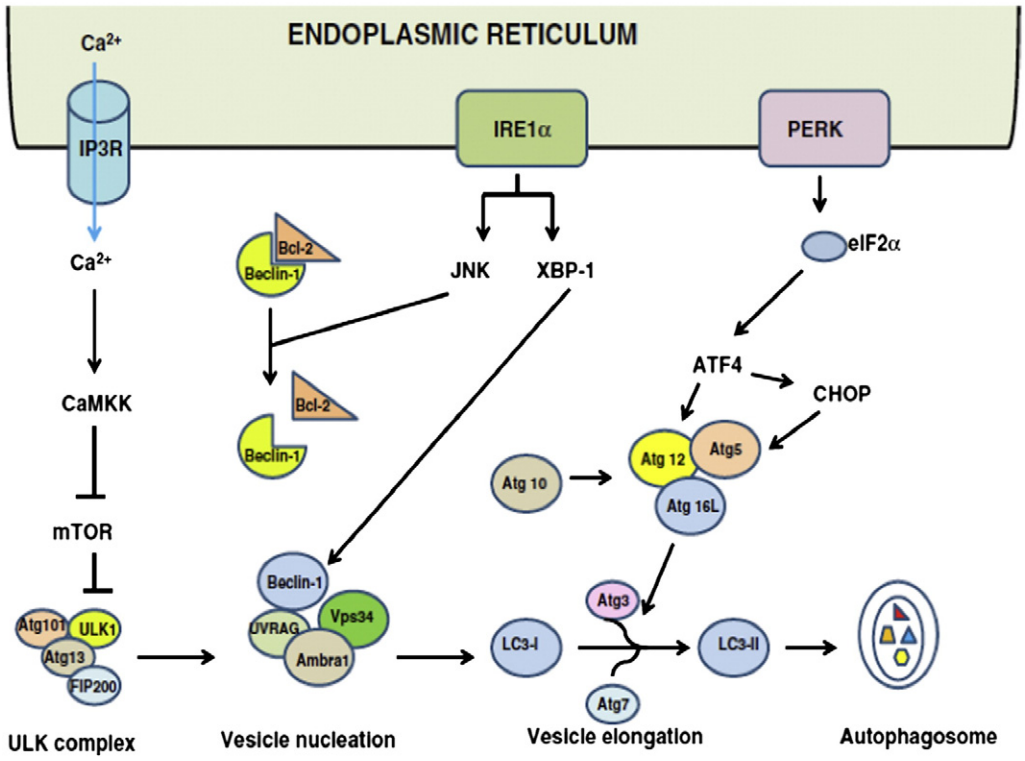

Fig. 4. ER stress can directly activate autophagy severely via three major signaling pathways, including (1) Ca^{2+}-dependent pathway, (2) the IRE1/JNK pathway and (3) PERK/eIF2α/ATF4-dependent pathway in the pathophysiological progress of many cardiovascular diseases. However, only the IRE1/JNK pathway has been demonstrated to take part in the induction of autophagy by the UPR in the diabetic heart. We still lack information about the relationship between autophagy and ER stress in the onset and progression of diabetic cardiomyopathy.

5.2. Apoptosis

In the pathogenesis of diabetic cardiomyopathy, ER stress develops in response to nascent protein misfolding in the ER lumen. A complex cellular response that occurs initially acts to promote the ER recovery, but, if the heart continues to be stressed, the UPR triggers apoptosis as the last measure to deal with the problem. This may ultimately result in heart failure and death. ER stress can directly induce cell apoptosis through two signaling pathways: the IREα/JNK pathway and the PERK/CHOP pathway. IRE1α modulates p38MAPK and extracellular regulated protein kinases (ERK) by binding to TRAF2, and this complex promotes apoptosis through JNK phosphorylation [104]. A dominant-negative form of XBP1 inhibits the XBP1-dependent arm of the UPR, leading to an increase in cardiomyocyte apoptosis during hypoxia [105]. Furthermore, several pro-apoptotic or anti-apoptotic proteins interact with IRE1α, regulating its activation state [106]. It was demonstrated that ASk1-null primary neurons were resistant to ER stress-induced cell apoptosis [107]. Activated ASK1 leads to JNK-mediated phosphorylation and activation of the pro-apoptotic protein binding to microtubule (Bim) [108], but inhibits Bcl-2 [109]. Our study proved that TM-induced myocardial ER stress, as evidenced by upregulation of BiP, CHOP, phosphorylated eIF2α/eIF2α, phosphorylated IRE1α/IRE1α, significantly increased the level of Bcl-2-associated X protein (Bax) and Bcl-2/Bax ratio with unchanged level of Bcl-2, while cardiac-specific overexpression of metallothionein can alleviate the myocardial contractile dysfunction and intracellular Ca^{2+} mishandling [101]. Thus, the formation of a macromolecular signaling complex of IRE1α with several pro-apoptotic proteins can generate apoptotic signals and establish an apoptotic environment.

During the pro-survival phase of ER stress, ATF4 induces numerous genes involved in resolution of the ER stress, such as genes that encode amino acid transporters and ER resident chaperones. However, sustained activation of the PERK pathway contributes to stress-induced cell apoptosis by ATF4-mediated induction of pro-apoptotic genes, including CHOP, ATF3, and GADD34. The induced transcription factor CHOP contributes to increased expression of the pro-apoptotic factors, such as death receptor 5 (DR5) [110], tribbles-related protein 3 (Trb3) [111], and Bim [112], and it can suppress Bcl-2 expression. The deletion of CHOP gene attenuates ER stress-induced apoptosis in cultured fibroblasts and partially protects mice from renal toxicity owing to pharmacological induction of ER stress by TM. A reduction in CHOP by knockout leads to an increase in cell survival and an alleviated oxidase stress [113]. Bim is also activated through protein phosphatase 2A-mediated dephosphorylation, which prevents its ubiquitination and proteasomal degradation [114]. However, ER stress is sustained due to the diabetic lesions and the abundance of Bip, PERK, CHOP, caspase-12, and JNK is significantly upregulated that results in the apoptosis of myocardial cells.

ER stress also induces the aberration of Ca^{2+} homeostasis, indirectly causing cardiomyocyte apoptosis. Heart failure is characterized by a decline in the force of contraction and dysregulation in intracellular Ca^{2+} homeostasis in myocyte [115]. Abnormal Ca^{2+} metabolism has been identified in both experimental diabetic models and diabetic patients. It involves a defect in one or more mechanisms that regulate intracellular Ca^{2+} concentration, including the sarcolemmal L-type Ca^{2+} channel, the sarcoplasmic reticulum (SR) Ca^{2+} release channel, the SERCA2a, the SERCA2a regulator phospholamban and the sarcolemmal Na^{+}/Ca^{2+} exchanger. Impaired calcium-handling proteins such as dissociation or downregulation of SERCA2a are linked to cardiac insufficiency in the diabetic heart [116]. It was reported that calcium-sensing receptor induced ER stress via the SR and mitochondrial death pathway which finally lead to cardiomyocyte apoptosis in the cardiac hypertrophy and heart failure [117]. Younce and colleagues proved that exendin-4 treatment reduced ER stress with the decreased expression of GRP78 and CHOP, leading to the enhancement of SERCA2a activity, then attenuated cardiomyocyte apoptosis [118]. To summarize,

four ER stress-dependent signaling pathways may participate in cardiomyocyte apoptosis during the pathophysiological progress of diabetic cardiomyopathy.

5.3. Insulin resistance

Insulin resistance is a major characteristic of obesity and type 2 DM and develops in multiple metabolic organs, including diabetic heart. Although lipid is utilized as the primary energy source in the heart, glucose becomes a critical energy source in the oxygen deficient state. In the diabetic heart, diminished activation of GLUT4 results in reduced glucose utilization and impaired insulin signaling, which may contribute to cardiomyocyte apoptosis and abnormal cardiac functions. Many potential drivers of cardiac insulin resistance have been found, including mitochondrial dysfunction, inflammation, cytokine upregulation and stress kinases signaling [119]. Recently, ER stress has emerged as a new player in this field and a considerable number of studies have pointed out its role in the onset of insulin resistance [120].

The UPR signaling pathways that mediate insulin action depend on a tyrosine-phosphorylation cascade, which begins with autophosphorylation of the insulin receptor tyrosine kinase, followed by tyrosine phosphorylation of proximal targets such as the IRS1 [121]. Earlier evidence revealed that Grp78-deficient mice were more responsive to insulin signaling following HFD feeding [122] with JNK1 being identified as an essential member of the growing network of serine kinases that inhibited insulin signaling [123]. Özcan and colleagues later discovered that ER stress induced the activation of this kinase through the transcription factor IRE1, or its downstream sensor XBP1 [75]. Further studies demonstrated that IRE1 activated JNK by recruiting TRAF2 and ASK1, and XBP1 activated the transcription of inflammatory genes that also directly contributed to the insulin resistance [104,124]. Dong and colleagues revealed that phosphorylated ER stress makers PERK (Thr980), IRE1, and eIF2α were significantly elevated in db/db mice and adiponectin, one of the adipocytokines with cardioprotection functions, can improve cardiomyocyte dysfunction in db/db mice through a mechanism possibly related to JNK and IRS1 [125]. Several studies have addressed the role of ER stress to mediate palmitate-induced insulin resistance in muscle cells. These findings conformed that TM-induced ER stress in C2C12 or L6 muscle cells led to a decrease in insulin signaling through phosphorylation of IRS1 by the IRE1/JNK pathway [126,127]. Recently, Hwang and colleagues demonstrated an important role for mTORC1-S6 kinase 1 (S6K1) pathway and showed that TM-induced ER stress could be prevented by pretreating cells with rapamycin, an mTORC1 inhibitor. Also, in S6K1 knockdown cells, TM induces ER stress through the S6K1-dependent mechanism in muscle [128]. Moreover, treatment with chemical chaperones such as 4-phenyl butyric acid or tauroursodeoxycholic acid has been shown to attenuate ER stress and to improve insulin sensitivity in diet-induced obese mice [129]. When insulin signaling is impaired during chronic hyperinsulinemia, the insulin growth factor (IGF)/Akt-induced cardiomyocyte hypertrophy may lead to a potential mismatch between cardiomyocyte size and vascularity contributing to relative hypoperfusion and increased stiffness in the phase of diastolic dysfunction. Indeed, the diabetic heart faces numerous stresses from hyperglycemia, hyperlipidemia and hyperinsulinemia, where insulin resistance may be a major intracellular event that predisposes the diabetic heart for its ultimate fate.

6. Clinical therapeutic perspectives

Maneuver to alleviate ER stress for the therapy against diabetic cardiomyopathy has drawn some attention despite many still remain at an early stage. First of all, using manipulations that up-regulate a protective UPR has been proven to possess the benefit for prolonged or severe ER stress in diabetic heart. As standard therapeutic modalities aiming at alleviating myocardial contractile dysfunction display various disadvantages in diabetic cardiomyopathy and its complications, UPR preconditioning, including activation of components of the adaptive pathway of UPR to deal with the stress or inhibition of the pro-apoptotic components of UPR, has demonstrated some promises for diabetic cardiomyopathy [68]. Secondly, certain low-molecular-weight chemical chaperones may possess therapeutic potentials for diabetic cardiomyopathy. Force and colleagues reported that proteasome inhibitors resulted in the accumulation of unfolded proteins to turn on UPR. Chemical ER chaperones such as 4-phenyl butyric acid may promote endogenous ER chaperone function in the heart and serve as ideal candidates to combat cardiotoxicity and harmful UPR response elicited by proteasome inhibitors [75]. Certain newly reported cardioprotective molecules, such as heavy metal scavenger metallothionein and mitochondrial aldehyde dehydrogenase (ALDH2), may also alleviate myocardial contractile anomalies induced by ER stress. These molecules may be developed as novel pro-survival therapeutic agents with clinical utility [101].

7. Conclusion

Given the important role of ER stress in the onset and progression of diabetic cardiomyopathy, it is imperative to understand the underlying mechanism through which ER stress evolves and affects diabetic hearts. Although a role for ER stress in the heart has received intensive attention over the recent years from both experimental and clinical perspectives, many questions remain unanswered: (1) The source(s) of ER stress in diabetic heart and whether they display cross-talk among them? (2) To what extent the adaptive and pro-apoptotic pathways of the UPR may be involved in the pathophysiology of diabetic cardiomyopathy? (3) Can ER stress be controlled in the context of diabetic myopathies? and (4) Should ER stress be considered a potential target for new drug discovery? Further studies are warranted to manipulate in vivo ER stress activation rather than supra-physiological activation of ER stress using chemical inducers. Given that chemical ER chaperones are capable of modulating ER stress, small molecules should hold the promises for future drug development to target on ER stress in diseases. Thus, identifying novel therapeutic targets to alleviate ER stress and restore ER homeostasis in the heart may be an essential step toward the management of diabetic cardiomyopathy.

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